INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 25 MAY 2004

			11 #12 7	VIFO			
Applicant's or agent's file reference PCB/PN/P89169PWO				FOR FURTHER ACTION	See Notification Preliminary Ex	n of Transmittal of international amination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 03/03159				International filing date (day/mol 23.07.2003	nth/year)	Priority date (day/month/year) 24.07.2002	
Interr	nationa	l Pate	nt Classification (IPC) or bo	oth national classification and IPC			
			61K38/55				
		-,				•	
Appli	icant			· · · · · · · · · · · · · · · · · · ·			
REN	RENOVO LIMITED et al						
			in ED of all			The state of the s	
 This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 							
2.	2. This REPORT consists of a total of 6 sheets, including this cover sheet.						
	This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).						
		•					
	Thes	se ani	nexes consist of a total of	of 2 sheets.			
					•		
3.	This I II II IV V VI VII VIII		Basis of the opinion Priority Non-establishment of Lack of unity of invent Reasoned statement citations and explanat Certain documents cit	under Rule 66.2(a)(ii) with regations supporting such statemen	ard to novelty, ir nt	and industrial applicability nventive step or industrial applicability;	
L							
Date	of sub	missi	on of the demand	Date	of completion of t	his report	
14.	14.01.2004			24.0	5.2004		
Nan	Name and mailing address of the international			nal Autho	rized Officer	ويعام الموادر	
preliminary examining authority: European Patent Office							
D-80298 Munich			80298 Munich	Dec	k, A	i o ll }	
Tel. +49 89 2399 - 0 Tx: 523 Fax: +49 89 2399 - 4465			91. +49 89 2399 - U 1X: 5231 9X: +49 89 2399 - 4465		hone No. +49 89	2300-8432	
1		_	· -	i colet	INU. THO 03	COURS COURS .	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/GB 03/03159

I.	Basis	of the	repor	l
----	--------------	--------	-------	---

1. With regard to the **elements** of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)):

	Des	scription, Pages				
	1-29	9	as originally filed			
	Cla	ims, Numbers				
	1-1:	3	received on 11.05.2004 with letter of 11.05.2004			
	Dra	wings, Sheets				
	1/4-	4/4	as originally filed			
2.	Witl lang	h regard to the langu guage in which the int	age, all the elements marked above were available or furnished to this Authority in the ternational application was filed, unless otherwise indicated under this item.			
	The	ese elements were av	ailable or furnished to this Authority in the following language: , which is:			
		the language of a tra	anslation furnished for the purposes of the international search (under Rule 23.1(b)).			
			lication of the international application (under Rule 48.3(b)).			
			anslation furnished for the purposes of international preliminant examination (under			
With regard to any nucleotide and/or amino acid sequence disclosed in the international application international preliminary examination was carried out on the basis of the sequence listing:						
		contained in the inte	mational application in written form.			
		filed together with th	e international application in computer readable form.			
		furnished subsequer	ntly to this Authority in written form.			
		furnished subsequently to this Authority in computer readable form.				
		The statement that t in the international a	he subsequently furnished written sequence listing does not go beyond the disclosure pplication as filed has been furnished.			
		The statement that t listing has been furn	he information recorded in computer readable form is identical to the written sequence ished.			
4.	The	amendments have r	esulted in the cancellation of:			
		the description,	pages:			
		the claims,	Nos.:			
		the drawings,	sheets:			

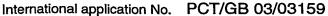
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/GB 03/03159

5.	This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).					
		(Any replacement sheet contain report.)	ning st	ıch amendm	ents must be referred to under item 1 and annexed to this	
6.	Additional observations, if necessary:					
IV.	Lac	k of unity of invention				
		-	ict or r	oav additiona	Il fees, the applicant has:	
 In response to the invitation to restrict or pay additional fees, the applicant has: 				· · · · · · · · · · · · · · · · · · ·		
		paid additional fees.			·	
		paid additional fees under prote	oot			
		•		•		
		neither restricted nor paid addi				
2.	This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.					
3.	This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is					
	×	complied with.				
		not complied with for the follow	ing re	asons:		
4.	Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:					
	☒	all parts.				
		the parts relating to claims No	s			
V.	 Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement 					
1.	Şta	Statement				
	No	velty (N)	Yes: No:	Claims Claims	1-13	
	Inv	entive step (IS)	Yes: No:	Claims Claims	1-13	
	Ind	ustrial applicability (IA)	Yes: No:	Claims Claims	1-13	
2	. Cit	ations and explanations				

see separate sheet



EXAMINATION REPORT - SEPARATE SHEET

Concerning section V

- 1. The following documents are referred to; the numbering will be adhered to in the rest of the procedure:
 - D1: GB-A-2 324 960 (UNIV MANCHESTER) 11 November 1998 (1998-11-11)
 - D2: WO 95 02579 A (ZENECA LTD ;CRAWLEY GRAHAM CHARLES (GB)) 26 January 1995 (1995-01-26)
 - D3: US-B1-6 262 020 (LEZDEY JOHN ET AL) 17 July 2001 (2001-07-17)
 - D4: US-A-5 439 824 (BRANTLY MARK ET AL) 8 August 1995 (1995-08-08)
 - D5: EP-A-0 968 723 (UNIV MANCHESTER) 5 January 2000 (2000-01-05)
 - D6: SHARON O'KANE ET AL: 'Transforming Growth Factor betas and Wound Healing' INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, EXETER, GB, vol. 29, no. 1, 1997, pages 63-78, XP008018620 ISSN: 1357-2725
 - D7: DUBOIS C ET AL: 'Processing of transforming growth factor beta 1 precursor by human furin convertase' JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 270, no. 18, 5 May 1995 (1995-05-05), pages 10618-10624, XP002115939 ISSN: 0021-9258 cited in the application
 - D8: SHAH M ET AL: 'Neutralisation of TGF-beta 1 and TGF-beta 2 or exogenous addition of TGF-beta 3 to cutaneous rat wounds reduces scarring.' JOURNAL OF CELL SCIENCE. ENGLAND MAR 1995, vol. 108 (Pt 3), March 1995 (1995-03), pages 985-1002, XP002260292 ISSN: 0021-9533
 - D9: CAMERON A ET AL: 'Polyarginines Are Potent Furin Inhibitors' JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 275, no. 47, 24 November 2000 (2000-11-24), pages 36741-36749, XP002251991 ISSN: 0021-9258
 - D10: TOMLINSON ANNETTE ET AL: 'Wound healing: a model of dermal wound repair.' METHODS IN MOLECULAR BIOLOGY (CLIFTON, N.J.) UNITED STATES 2003, vol. 225, 2003, pages 249-260, XP001156105 ISSN: 1064-3745

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

2. Novelty

w 2.

D1, from the inventor of the present application, discloses the delivery of DNA encoding agents which neutralize a growth factor at a wound site, to inhibit scarring and fibrosis. Such agents are e.g. convertase (serine protease) inhibitors. which neutralize e.g. TGF-β1 or TGF-β2. D1 does not specify furin inhibitors among these agents.

D2 discloses the use of TNF convertase inhibitors for the treatment of TNF related diseases, e.g. pulmonary fibrosis or cirrhosis. D2 does not disclose the use of furin inhibitors.

D3 discloses the topical use of the convertase inhibitor alpha 1- antitrypsin for wound healing with prevention of scarring; D4 discloses the topical (lung) use of a DNA molecule encoding AAT to treat e.g. cystic fibrosis.

It is not clear for the time being whether AAT is a furin inhibitor, hence the subjectmatter of the present claims seems to be novel.

However, for the sake of clarity, the applicant should expect to be asked, when entering the national phase, to provide a statement that AAT is not a furin inhibitor, to indicate which inhibitors listed in the application are specific for furin, and to delete all other inhibitors from the application.

In addition, the applicant should be prepared to delete claim 2 as it renders the scope of claim 1 on which it depends unclear.

3. Inventive activity

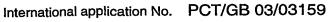
The closest prior art is the document D5, from the inventor of the present application, which discloses the use of antibodies which diminish the activity of TGF- β 1, for preventing scarring and fibrosis.

The inventors have now discovered that the convertase furin is responsible for the extracellular activation of platelet large latent TGF-B1 complex in the surrounding tissue following degranulation of platelets.

The difference over the closest prior art is the modulation of furin instead of a direct modulation of TGF-β1 by e.g. antibodies.

The problem is therefore to find an alternative way of preventing TGF-β1 activity, thereby preventing scarring or fibrosis.

The application solves the problem by the use of the furin inhibitors decanoyl-



EXAMINATION REPORT - SEPARATE SHEET

RVKR-cmk or hexa-arginine.

It is known from the prior art that furin is responsible for the activation of pro-TGF- $\beta 1$ (see D7). It is also known from the prior art that TGF- $\beta 1$ and TGF- $\beta 2$ but not $\mathsf{TGF}\text{-}\beta3$ are responsible for scarring and fibrosis (see D6 and D8 from the inventor).

However, the discovery by the inventor that the furin inhibitor dec- RVKR-cmk reduces the generation of active TGF- $\beta 1$ in vitro at the site of platelet activation could not be foreseen by the skilled person. Hence the subject-matter of the present claims seems to involve an inventive step.